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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,023	10/27/2000	Gang Chen	UTSB:675US/SLH	5751

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EXAMINER	
FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	

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12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/699,023	CHEN ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) *33-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Office Action is responsive to Applicant's response filed July 19, 2002. Claim 30 has been amended. The submission of Appendices A-D is acknowledged. Appendix A, a marked up copy of the amendments. Appendix B, a copy of page 31 of the specification. Appendix C, a definition of the term "capable of" from the online version of Encarta Dictionary and Appendix D, a definition of the term "capable of" from the online version of Merriam-Webster's Collegiate Dictionary.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

3. In view of Applicant's amendment the following Objections and Rejections have been withdrawn:

a) Objection to the specification, page 2, paragraph 2 of previous Office action.
b) Objection to the specification, page 2, paragraph 3 of previous Office action.
c) Objection to the specification, page 2, paragraph 4, of previous Office action.
d) Objection to the claims, page 2, paragraph 5, of previous Office action.
e) Objection to the drawing, page 3, paragraph 6, of previous Office action.
f) Rejection of claims 1,2,4,7,13 and 22 under 35 U.S.C. 112, second paragraph, page 3, paragraph 7 of previous Office action.
g) Rejection of claims 1-32 under 35 U.S.C. 102(b), pages 3-4, paragraph 8 of the previous Office action.

Objections/Rejections Maintained

4. In view of Applicant's amendment concerning formal matters the objections to the drawings are maintained for the reasons set forth on page 3, paragraph 6 of the previous Office Action.

The objection to the drawings was on the grounds that the drawings are objected to by the Draftsman under 37 CFR 1.84 or 1.152. See the attached form PTO 948.

Applicant must submit formal drawing, please see the attachment. There has been no receipt of corrected formal drawings. Therefore, the objections are maintained for reasons of record.

5. The rejection of claims 1-25 and 27-32 under 35 U.S.C. 102(b) as being anticipated by Georgiou is maintained for the reasons set forth on pages 6-8, paragraph 9 of the previous Office Action.

The rejection was on the grounds that Georgiou teaches a method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein capable of binding a target ligand comprising the steps of: Obtaining antibodies from an expression vector library that may be prepared from DNAs encoding antibodies or antibody fragments, selecting the antigen one desires to identify and isolating specific antibody or antibodies which are labeled with detectable labels, which includes fluorescent labels (column 5, lines 40-65). Georgiou teaches that the preferred are host cells from gram-negative bacteria such as *E. coli* (column 7, lines 50-53). Georgiou teaches that *E. coli* cultures were grown at 24°C or 37°C (column 22, lines 61-64). Georgiou teaches that identifying the antibody or antibody fragment expressing cells may be accomplished by methods that depend on detecting the presence of the bound detectable label. Georgiou teaches that a preferred identification and isolation is cell sorting or flow cytometry and that one aspect of this method is fluorescence activated cell sorting (FACS) (column 6, lines 4-9). Georgiou teaches that the analyte (candidate binding protein) of particular interest are amino acids, peptides, proteins, lipids, saccharides, nucleic acids and combinations thereof (column 6, lines 32-50). Georgiou teaches that a particular advantage of cell surface (periplasm) expressed antigen-binding antibodies is that the antibody is attached to the outer membrane of the cell

(column 6, lines 63-65) and that the surface displayed antibodies or antibody conjugates may be catalytic antibodies or antibody conjugates such as fusion protein that include reporter molecules, e.g. alkaline phosphatase, luciferase and β-lactamase (column 8, lines 54-63). Georgiou teaches that the cells with the antibody displayed on the surface may themselves be attached to a solid support such as a membrane, dipstick or beads to further facilitate removal of the cells (column 7. lines 2-5). Georgiou et al teach that detectable labels that may be used in the invention are radioactive, fluorescent, chemiluminescent and electrochemiluminescent agents (column 8, lines 35-42). Georgiou et al teach that cells were harvested and resuspended in PBS pH 7.4 at a concentration of 10^{10} cell/ml based on the $O.D._{600}$ to form a cell shock and some cells were resuspended in 15 % glycerol /water and stored at 70°C (i.e. hyperosmotic conditions and physical stress) (column 39, lines 40-47). Limitations such as the ligand comprise a molecular weight of less than about 20,000 Da, less than about 5,000 Da and a molecular weight greater than 600 Da and less than about 30,000 Da would be inherent in the teachings of the prior art.

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that Georgiou does not teach expression of a binding protein in soluble form in a bacterium. Applicant urges that Georgiou does not teach contacting a gram-negative bacterium with a labeled ligand capable of diffusing into the bacterium. Applicant urges that Georgiou does not teach selecting a bacterium based on the presence of labeled ligand within the bacterium, wherein the ligand and a candidate binding protein are bound in the bacterium. Applicant urges that Georgiou does not teach the claim limitations or such a rationale to one could conclude that such a teaching has been made.

Applicant's arguments filed July 19, 2002 have been fully considered but they are not persuasive.

It is the Examiner's position that Georgiou anticipates the claimed invention. It is the Examiner's position that Georgiou teaches expression of a binding protein in soluble form in a bacterium. Column 6, lines 4-15 disclose that the identification of antibody expressing bacteria by fluorescence activated cell sorting (FACS) is used to identify the antibodies of the invention. Georgiou teaches that identification of antibody expressing FACS is directly based on the affinity for the soluble hapten thus eliminating artifacts due to binding in solid surfaces. Therefore, one could reasonable conclude that Georgiou teaches expression of a binding protein in soluble form in a bacterium because FACS is used as a method of identifying the antibodies in the invention and FACS requires the use of soluble haptens.

It is the Examiner's position that Georgiou teaches contacting a gram-negative bacterium with a labeled ligand capable of diffusing into the bacterium. Columns 5, lines 40-67 and column 6, lines 1-3 disclose that screening for antibodies employing methods of the invention allows one to select an antibody or antibody fragment from a plurality of candidate antibodies that have been expressed on the surface of a host cell. Column 7, lines 14-34 disclose that host cells are contacted with a standard analyte sample that contains a known amount of an analyte linked to a detectable label employing conditions effective for forming an immune complex. Georgiou teaches that in actual assay a known amount of antibody-covered cells are placed in a solution of a known concentration of the analyte-conjugate along with an unknown concentration of the analyte and the analyte –conjugate competes with free analyte for binding to the antibody molecules on the cell surface. One could reasonably conclude that the labeled

ligand is capable of diffusing into the bacterium since immunocomplexes are formed and that the immunocomplexes are bound to the bacterium since the detection occurs at the cell surface of the bacterium.

It is the Examiner's position that claimed invention is the same as the invention of the prior since the Applicant has provided no side-by-side comparison to show that the claimed method and the method of the prior art are different.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Georgiou *(U.S. Patent No. 5,866, 344, published February 2, 1999)* in view of Pini et al *(The Journal of Biological Chemistry,1998, Vol. 273, No. 34, p. 21769-21776).*

Claims 1-32 are drawn to a method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein capable of binding a target ligand comprising the steps of: providing a gram-negative bacterium comprising a nucleic acid sequence encoding a candidate binding protein, wherein said binding protein is expressed in

soluble form in said bacterium; contacting said bacterium with a labeled ligand capable of diffusing into said bacterium; and selecting said bacterium based on the presence of said labeled ligand within the bacterium, wherein said ligand and said candidate binding protein are bound in said bacterium.

Georgiou teaches a method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein capable of binding a target ligand comprising the steps of: Obtaining antibodies from an expression vector library that may be prepared from DNAs encoding antibodies or antibody fragments, selecting the antigen one desires to identify and isolating specific antibody or antibodies which are labeled with detectable labels, which includes fluorescent labels (column 5, lines 40-65). Georgiou teaches that the preferred are host cells from gram-negative bacteria such as *E. coli* (column 7, lines 50-53). Georgiou teaches that *E. coli* cultures were grown at 24°C or 37°C (column 22, lines 61-64). Georgiou teaches that identifying the antibody or antibody fragment expressing cells may be accomplished by methods that depend on detecting the presence of the bound detectable label. Georgiou teaches that a preferred identification and isolation is cell sorting or flow cytometry and that one aspect of this method is fluorescence activated cell sorting (FACS) (column 6, lines 4-9). Georgiou teaches that the analyte (candidate binding protein) of particular interest are amino acids, peptides, proteins, lipids, saccharides, nucleic acids and combinations thereof (column 6, lines 32-50). Georgiou teaches that a particular advantage of cell surface (periplasm) expressed antigen-binding antibodies is that the antibody is attached to the outer membrane of the cell (column 6, lines 63-65) and that the surface

displayed antibodies or antibody conjugates may be catalytic antibodies or antibody conjugates such as fusion protein that include reporter molecules, e.g. alkaline phosphatase, luciferase and β-lactamase (column 8, lines 54-63). Georgiou teaches that the cells with the antibody displayed on the surface may themselves be attached to a solid support such as a membrane, dipstick or beads to further facilitate removal of the cells (column 7. lines 2-5). Georgiou et al teach that detectable labels that may be used in the invention are radioactive, fluorescent, chemiluminescent and electrochemiluminescent agents (column 8, lines 35-42). Georgiou et al teach that cells were harvested and resuspended in PBS pH 7.4 at a concentration of 10^{10} cell/ml based on the $O.D._{600}$ to form a cell shock and some cells were resuspended in 15 % glycerol /water and stored at 70°C (i.e. hyperosmotic conditions and physical stress) (column 39, lines 40-47).

Georgiou do not teach the use of filamentous phages.

Pini et al teach the use of phages in constructing antibody libraries (see the Abstract). Pini et al teach that phage antibody display technology is simple, inexpensive and lends itself to simultaneous processing of several antigens (page 21769, 2nd column) and that synthetic antibody repertoires constructed with a single germ line segment have reliably yielded good binders against a large variety of antigens (page 21774, 1st column).

It would be *prime facie* obvious at the time the invention was made to treat the bacterium used in the methods of screening antibody libraries as taught by Georgiou et al with phages as taught by Pini et al because Pini et al that phage antibody display

technology is simple, inexpensive and lends itself to simultaneous processing of several antigens (page 21769, 2nd column) and that synthetic antibody repertoires constructed with a single germ line segment have reliably yielded good binders against a large variety of antigens (page 21774, 1st column). It would be expected barring evidence to the contrary that the use of phage antibody technology can be used to produce large functional antibody libraries and because several biological applications high-affinity binders are needed the phage library may be constructed in a way that allows the facile affinity maturation of antibodies of interest (page 21769, 2nd column).

Status of Claims

7. No claims are allowed.

Conclusion

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
October 15, 2002

MARK NAVARRO
PRIMARY EXAMINER